PRODUCT INFORMATION

PRALUENT ®

NAME OF THE MEDICINE

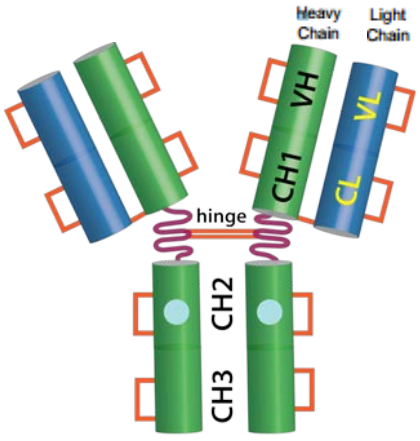
AUSTRALIAN APPROVED NAME

Alirocumab (rch)

STRUCTURE

Alirocumab consists of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a fully human kappa light chain. A single N-linked glycosylation site is located in each heavy chain within the CH2 domain of the Fc constant region of the molecule. The variable domains of the heavy and light chains combine to form the proprotein convertase subtilisin kexin type 9 (PCSK9) binding site within the antibody. Alirocumab has an approximate molecular weight of 146 kDa.

Figure 1 - Schematic representative of the structure of alirocumab



CH = constant region of the heavy chain; CL = constant region of the light chain; VH = variable region of the heavy chain; VL = variable region of the light chain.

CAS REGISTRY NUMBER

1245916-14-6

DESCRIPTION

Alirocumab is a fully human monoclonal antibody (IgG1 isotype) that targets PCSK9. Alirocumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

Alirocumab is a sterile, clear, colourless to pale yellow solution for subcutaneous injection with pH of about 6.0, containing no antimicrobial preservatives. Praluent 75 mg/mL and 150 mg/mL solution for injection in a single-use pre-filled pen or single-use pre-filled syringe is supplied in a siliconised 1.0 mL Type I clear glass syringe. The rubber shield does not contain natural latex.

Each 1.0 mL single-use pre-filled pen or pre-filled syringe contains 75 mg or 150 mg alirocumab and the following excipients: histidine, sucrose, polysorbate 20 and water for injection.

PHARMACOLOGY

Alirocumab inhibits PCSK9 activity in both *in vitro* assays and *in vivo* model systems. Many studies in animals and humans have demonstrated the central role that elevated levels of LDL-C play in the initiation and progression of atherosclerosis.

Mechanism of Action

Alirocumab binds with high affinity and specificity to PCSK9 which binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote their degradation. LDLR is the primary receptor that clears circulating low-density lipoprotein (LDL), therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of low-density lipoprotein cholesterol (LDL-C). By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

In genetic studies in humans, PCSK9 variants with either loss-of-function or gain-of-function mutations have been identified. Individuals with single allele PCSK9 loss-of-function mutation have lower levels of LDL-C, which correlated with a significantly lower incidence of coronary heart disease. A few individuals have been reported, who carry PCSK9 loss-of-function mutations in two alleles and have profoundly low LDL-C levels, with HDL-C and TG levels in the normal range. Conversely, gain-of-function mutations in the PCSK9 gene have been identified in patients with increased LDL-C levels and a clinical diagnosis of familial hypercholesterolaemia (FH).

Observational analyses have demonstrated that the untreated LDL-C levels in patients with gain-of-function mutations in the PCSK9 gene are in a similar range to those observed in patients with the more traditional mutations that cause heterozygous FH (heFH) (such as in the LDLR gene) demonstrating a central role for PCSK9 in LDL-C metabolism and levels. In a multicentre, double-blind, placebo-controlled, 14 week study, 13 patients with heFH due to gain-of-function mutations in the PCSK9 gene were randomised to receive either alirocumab 150 mg once every 2 weeks or placebo. Mean baseline LDL-C was 3.92 mmol/L. At week 2, the mean reduction from baseline in LDL-C was 62.5% in the alirocumab-treated patients as compared to 8.8% in the placebo patients. At week 8, the mean reduction in LDL-C from baseline with all patients treated with alirocumab was 72.4%.

Pharmacodynamic effects

In *in vitro* assays, alirocumab did not induce Fc-mediated effector function activity (antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity) either in the presence or absence of PCSK9 and no soluble immune complexes capable of binding complement proteins were observed for alirocumab when bound to PCSK9.

The pharmacodynamic effect of alirocumab in lowering LDL-C is indirect, and mediated through the binding to PCSK9. A concentration-dependent reduction in free PCSK9 and LDL-C is observed until target saturation is achieved. Upon saturation of PCSK9 binding, further increases in alirocumab concentrations do not result in a further LDL-C reduction, however an extended duration of the LDL-C lowering effect is observed.

PHARMACOKINETICS

Absorption

After subcutaneous administration of 50 mg to 300 mg alirocumab, median times to maximum serum concentration (t_{max}) were 3-7 days. The pharmacokinetics of alirocumab after single subcutaneous administration of 75 mg into the abdomen, upper arm or thigh were similar. The absolute bioavailability of alirocumab after subcutaneous administration was 85% as determined by population pharmacokinetic analysis. A slightly greater than dose proportional increase was observed, with a 2.1- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose. Steady state was reached after 2 to 3 doses with an accumulation ratio of about 2-fold.

Distribution

Following intravenous administration, the volume of distribution was about 0.04 to 0.05 L/kg indicating that alirocumab is distributed primarily in the circulatory system.

Metabolism

Specific metabolism studies were not conducted, because alirocumab is a protein. Alirocumab is expected to degrade to small peptides and individual amino acids.

Elimination

Two elimination phases were observed for alirocumab. At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination of alirocumab is largely through a non-saturable proteolytic pathway.

Based on a population pharmacokinetic analysis, the median apparent half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab as monotherapy at subcutaneous doses of either 75 mg once every 2 weeks or 150 mg once every 2 weeks. When co-administered with a statin, the median apparent half-life of alirocumab was 12 days.

Special Populations

Gender

Based on a population pharmacokinetic analysis, gender has no impact on alirocumab pharmacokinetics.

Elderly

In controlled studies, 1158 patients (34.7%) treated with Praluent were ≥ 65 years of age, 241 patients (7.2%) treated with Praluent were ≥ 75 years of age. Based on a population pharmacokinetic analysis, age was associated with a small difference in alirocumab exposure at steady state, with no impact on efficacy or safety.

Paediatric

The pharmacokinetic effects of alirocumab administration in pediatric patients have not been studied.

Race

Based on a population pharmacokinetic analysis, race had no impact on alirocumab pharmacokinetics. Following single-dose subcutaneous administration of 100 mg to 300 mg alirocumab, there was no meaningful difference in exposure between Japanese and Caucasian healthy subjects.

Body weight

Based on a population pharmacokinetic analysis, body weight had a small impact on alirocumab exposure, with no effect on efficacy or safety.

Hepatic Impairment

In a phase 1 study, after administration of a single 75 mg subcutaneous dose, alirocumab pharmacokinetic profiles in subjects with mild and moderate hepatic impairment were similar as

compared to subjects with normal hepatic function. No data are available in patients with severe hepatic impairment.

Renal Impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of alirocumab. Population pharmacokinetic analyses showed that mild and moderate renal impairment did not have a meaningful impact on alirocumab pharmacokinetics. No data are available in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73m^2).

CLINICAL TRIALS

The efficacy of Praluent was investigated in ten phase 3 trials (five placebo-controlled and five ezetimibe-controlled studies), involving 5,296 randomised patients with 3,188 patients randomised to Praluent. The five placebo-controlled trials involved 3,499 patients of which 36% were patients with heterozygous familial hypercholesterolemia (heFH) and 54% were non-FH patients who had clinical atherosclerotic cardiovascular disease. Three of the ten studies were conducted exclusively in patients with heterozygous familial hypercholesterolaemia (heFH). The majority of patients in the phase 3 program were taking background lipid-modifying therapy (LMT) consisting of a maximally tolerated dose of statin, with or without other lipid-modifying therapies, and were at high or very high cardiovascular (CV) risk. Two studies were conducted in patients who were not concomitantly treated with a statin, including one study in patients with documented statin intolerance. Alirocumab has not been studied in patients with homozygous familial hypercholesterolaemia.

Eight studies were performed with a dose of 75 mg once every 2 weeks, and criteria-based up-titration to 150 mg once every 2 weeks at week 12 in patients who did not achieve their pre-defined target LDL-C based on their level of CV risk at week 8. Two studies (LONG TERM and HIGH FH), involving a total of 2,416 patients, were performed with a 150 mg once every 2 week dose only. Baseline demographic characteristics were well matched between the Praluent and control groups. The age of the patients ranged from 18 to 89 years across studies (mean age 60 years); 38% were women; the majority of patients were Caucasians (90%), 5% were Black, 2% were Asian; the mean body mass index (BMI) was 30 kg/m2. In the phase 3 studies, 31% of patients had type 2 diabetes mellitus, and 64% of patients had a history of coronary heart disease.

The primary efficacy endpoint in all of the phase 3 studies was the mean percent reduction from baseline in LDL-C at week 24 as compared to placebo or ezetimibe. All of the studies met their primary endpoint. The effect of Praluent on cardiovascular morbidity and mortality is currently being investigated in an ongoing clinical trial in 18,000 patients (OUTCOMES).

In general, administration of Praluent also resulted in a statistically significant greater percent reduction in Total-C, non-HDL-C, Apo B, and Lp(a) as compared to placebo/ ezetimibe, whether or not patients were concomitantly being treated with a statin. Praluent also reduced triglycerides, and increased HDL-C and Apo A-1 as compared to placebo.

Reduction in LDL-C was seen across age, gender, body mass index (BMI), race and baseline LDL-C levels. LDL-C reduction was consistent regardless of concomitantly used statins and doses. A significantly higher proportion of patients achieved an LDL-C of <1.81 mmol/L in the Praluent group as compared to placebo or ezetimibe at week 12 and week 24. In studies using the criteria-based up-titration regimen, a majority of patients achieved the pre-defined target LDL-C (based on their level of CV risk) on the 75 mg once every 2 weeks dose, and a majority of patients maintained treatment on the 75 mg once every 2 week dose.

The lipid-lowering effect of Praluent was observed within 15 days after the first dose reaching maximum effect at approximately 4 weeks. Efficacy was sustained over the duration of study treatment (up to 78 weeks in the LONG TERM study). Following discontinuation of Praluent, no rebound in LDL-C was observed, and LDL-C levels gradually returned to baseline levels.

Table 1 summarises the mean percent change from baseline in LDL-C with Praluent at week 12 (before up-titration) and at week 24 (primary endpoint) based on analyses across pooled phase 3 studies.

Table 1 - Mean percent change from baseline in LDL-C with alirocumab at week 12 (before up-titration) and week 24 (primary endpoint) in analyses of pooled phase 3 studies in patients on background statin[a]

Week 12	Placebo controlled studies		Ezetimibe controlled studies	
Dose	Praluent (additive effect beyond statin)	Placebo (additive effect beyond statin)	Praluent (additive effect beyond statin)	Ezetimibe (additive effect beyond statin)
75 mg	-44.5	4.1	-49.2	-22.3
150 mg	-62.6	1.1	-	-

Week 12	**Placebo controlled studies**		**Ezetimibe controlled studies**	
Week 24				
Dose	Praluent (additive effect beyond statin)	Placebo (additive effect beyond statin)	Praluent (additive effect beyond statin)	Ezetimibe (additive effect beyond statin)
75/150 mg (up-titration studies)[b]	-48.6	4.2	-48.9	-19.3
150 mg	-60.4	0.5	-	-

[a] Based on ITT analysis - intent-to-treat population, includes all lipid data throughout the duration of the study irrespective of adherence to the study treatment.

[b] Dose was up-titrated to 150 mg once every 2 weeks in 228 (34.5%) patients treated beyond 12 weeks.

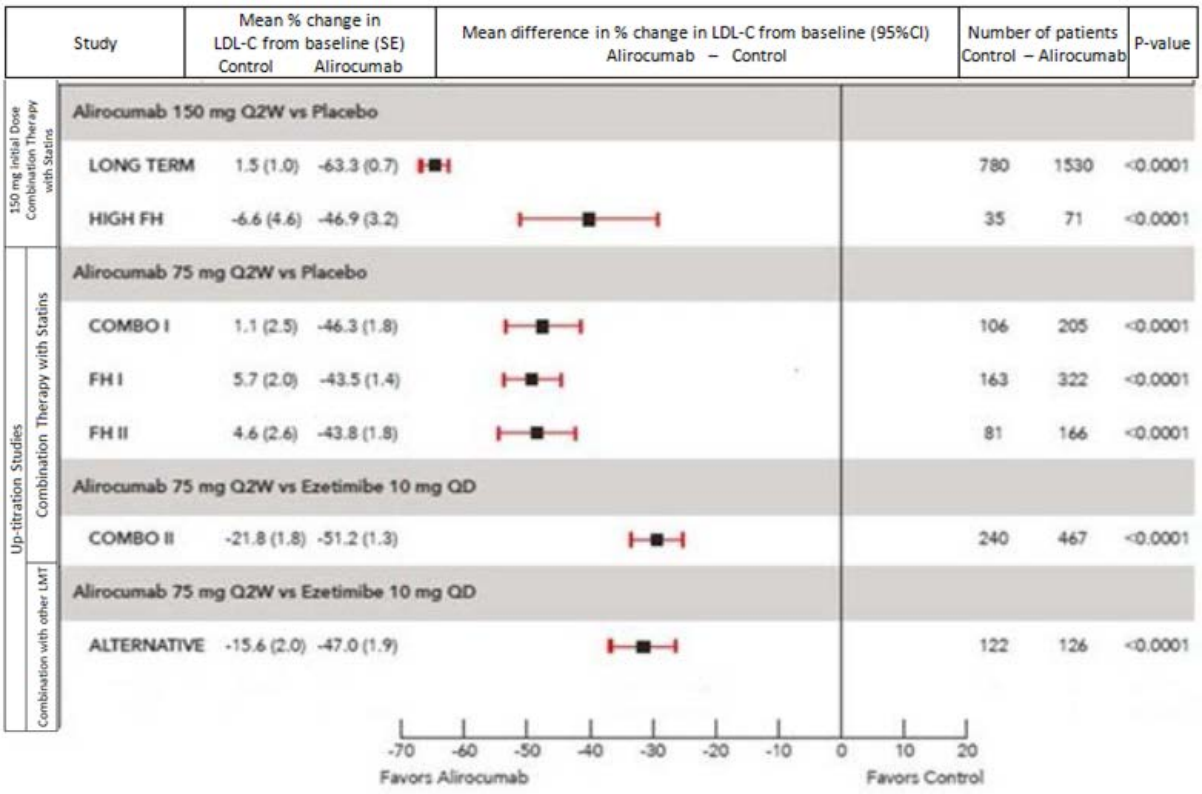
Baseline LDL-C in analyses of pooled up-titration studies (COMBO I, FH I and FH II) was 3.33 mmol/L in the Praluent group and 3.36 mmol/L in the placebo group.

Baseline LDL-C in analyses of pooled studies using the 150 mg once every 2 weeks dose (LONG TERM, HIGH FH) was 3.26 mmol/L in the Praluent group and 3.24 mmol/L in the placebo group.

The individual results for each of the studies are included below.

Figure 2 summarises the mean reduction from baseline in LDL-C with Praluent at week 12 (before up-titration) across phase 3 studies. This figure shows the efficacy of the 75 mg once every 2 week and 150 mg once every 2 week doses. Week 24 results are provided in the description of the individual studies.

Figure 2 - Summary of mean reduction from baseline in LDL-C with Praluent at week 12 (before up-titration) across phase 3 studies.



COMBINATION THERAPY WITH A STATIN

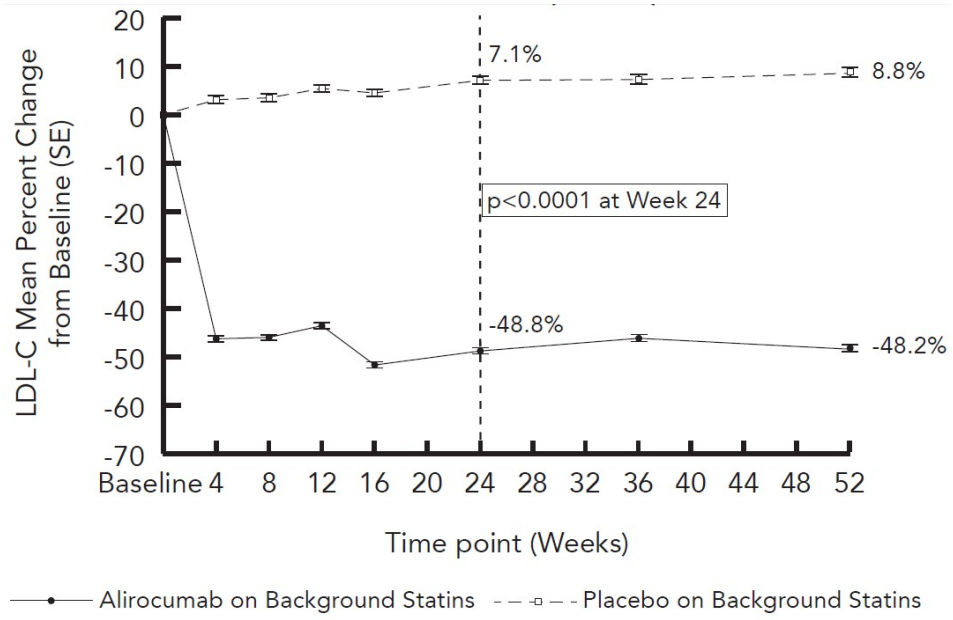
Placebo-controlled phase 3 studies

FH I and FH II studies

Two multicentre, placebo-controlled, double-blind 18-month studies included 732 patients (488 in the Praluent group and 244 patients in the placebo group, with a majority of patients treated for a minimum of 52 weeks) with heFH receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either Praluent 75 mg once every 2 weeks or

placebo in addition to their existing lipid modifying therapy. Dose up-titration of Praluent to 150 mg once every 2 weeks occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -55.8% (95% CI: -60.0%, -51.6%; p-value: < 0.0001). At week 12 (before up-titration), 50.2% of patients reached an LDL-C of <1.81 mmol/L as compared to 0.6% in the placebo group. Among the subgroup of patients up-titrated at week 12, an additional 15.7% mean reduction in LDL-C was achieved at week 24. See Table 2 and Figure 3 for details.

Figure 3 - LDL-C over time: Mean percent change from baseline up to 52 weeks – pool of FH studies (FH I and FH II) (ITT analysis)



HIGH FH study

A third multicentre, double-blind, placebo-controlled 18-month study included 106 heFH patients (71 patients in the Praluent group and 35 patients in the placebo group with a majority of patients treated for a minimum of 52 weeks) on a maximally tolerated dose of statin, with or without other lipid-modifying therapies, and a baseline LDL-C ≥ 4.14 mmol/L. Patients received either Praluent at a dose of 150 mg once every 2 weeks or placebo in addition to their existing lipid-modifying therapy. Mean baseline LDL-C was 5.08 mmol/L in the Praluent group and 5.20 mmol/L in the

placebo group. The mean percent change from baseline with Praluent in LDL-C (ITT analysis) was -46.9% at week 12 and -45.7% at week 24 compared to -6.6% at week 12 and -6.6% at week 24 for placebo. This corresponded to a mean absolute change from baseline at week 24 of -2.35 mmol/L. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -39.1% (95% CI: -51.1%, -27.1%; p-value: <0.0001). Mean changes for all other lipids/lipoproteins were similar to the FH I and FH II studies, however statistical significance was not reached for TG, HDL-C and Apo A-1. See Table 2 for details.

COMBO I study

A multicentre, double-blind, placebo-controlled, 52 week study included 311 patients (205 in the Praluent group and 106 in placebo group) categorised as very high CV risk and not at their pre-defined target LDL-C on a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either 75 mg Praluent once every 2 weeks or placebo in addition to their existing lipid-modifying therapy. Dose up-titration of Praluent to 150 mg once every 2 weeks occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L. Mean baseline LDL-C was 2.59 mmol/L in the Praluent group and 2.74 mmol/L in the placebo group. The mean percent change from baseline with Praluent in LDL-C (ITT analysis) was -46.3% at week 12 and -48.2% at week 24 compared to 1.1% at week 12 and -2.3% at week 24 for placebo. This corresponded to a mean absolute change from baseline at week 24 of -1.30 mmol/L. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -45.9% (95% CI: -52.5%, -39.3%; p-value: <0.0001). At week 12 (before up-titration), 76.0% of patients in the Praluent group reached an LDL-C of < 1.81 mmol/L as compared to 11.3% in the placebo group. The dose was up-titrated to 150 mg once every 2 weeks in 32 (16.8%) patients treated beyond 12 weeks. Among the subgroup of patients up-titrated at week 12, an additional 22.8% mean reduction in LDL-C was achieved at week 24. The difference versus placebo was statistically significant at week 24 for all lipids/ lipoproteins except TG and Apo A-1. See Table 2 for details.

Ezetimibe-controlled phase 3 study (on background statin)

COMBO II study

A multicentre, double-blind, ezetimibe-controlled 2 year study included 707 patients (467 patients in the Praluent group and 240 patients in the ezetimibe group, with a majority of patients treated for a minimum of 52 weeks) categorised as very high CV risk and not at their pre-defined target LDL-C on a maximally tolerated dose of statin. Patients received either Praluent 75 mg once

every 2 weeks or ezetimibe 10 mg once daily in addition to their existing statin therapy. Dose up-titration of Praluent to 150 mg once every 2 weeks occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L. At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -29.8% (95% CI: -34.4%, -25.3%; p-value: <0.0001). At week 12 (before up-titration), 77.2% of patients reached an LDL-C of < 1.81 mmol/L as compared to 46.2% in the ezetimibe group. Among the subgroup of patients up-titrated at week 12, an additional 10.5% mean reduction in LDL-C was achieved at week 24. See Table 2 for details.

STATIN INTOLERANT THERAPY (ADD-ON TO NON-STATIN LIPID MODIFYING THERAPY)

ALTERNATIVE study

A multicentre, double-blind, ezetimibe-controlled, 24 week study included 248 patients (126 patients in the Praluent group and 122 in the ezetimibe group) with documented statin intolerance due to skeletal muscle-related symptoms. Patients received either Praluent 75 mg once every 2 weeks or ezetimibe 10 mg once daily, or atorvastatin 20 mg once daily (as a re-challenge arm). Dose up-titration of Praluent to 150 mg once every 2 weeks occurred at week 12 in patients with LDL-C ≥ 1.81 mmol/L or ≥ 2.59 mmol/L, depending on their level of CV risk. At week 24, the mean treatment difference from ezetimibe in LDL-C percent change from baseline was -30.4% (95% CI: -36.6%, -24.2%; p-value: <0.0001). At week 12 (before up-titration), 34.9% of patients achieved an LDL-C of < 1.81 mmol/L as compared to 0% in the ezetimibe group. Among the subgroup of patients up-titrated at week 12, an additional 3.6% mean reduction in LDL-C was achieved at week 24.

This trial evaluated patients who did not tolerate at least two statins (at least one at the lowest approved dose), and enrolled only patients willing to be re-challenged with a statin. The statin re-challenge arm was included to further validate the diagnosis of statin intolerance in a blinded manner. In these patients with a history of statin intolerance, musculoskeletal adverse events occurred at a lower rate in the Praluent group (32.5%) as compared to the atorvastatin group (46.0%) (HR= 0.61 [95% CI, 0.38 to 0.99]), and a lower percentage of patients in the Praluent group (15.9%) discontinued study treatment due to musculoskeletal adverse events as compared to the atorvastatin group (22.2%). These discontinuation rates due to musculoskeletal adverse events in the ALTERNATIVE study were higher than in other phase 3 studies. In the five placebo-controlled trials in patients on a maximally tolerated dose of statin (n=3752), the discontinuation rate due to musculoskeletal adverse events was 0.4% in the Praluent group and 0.5% in the placebo group. See Table 2 for details.

LONG-TERM EFFICACY IN PRIMARY HYPERCHOLESTEROLAEMIA

LONG TERM study

This multicentre, double-blind, placebo-controlled, 18-month study included 2,310 patients (1,530 patients in the Praluent group and 780 patients in the placebo group) with primary hypercholesterolaemia at high or very high CV risk and on a maximally tolerated dose of statin, with or without other lipid-modifying therapy. Patients received either Praluent at a dose of 150 mg once every 2 weeks or placebo in addition to their existing lipid-modifying therapy. The LONG TERM study included 17.7% heFH patients, 34.6% with type 2 diabetes mellitus, and 68.6% with a history of coronary heart disease. Mean treatment duration was 64.6 weeks, with a majority of patients treated for a minimum of 52 weeks, and 607 patients with 18-month data analysed. At week 24, the mean treatment difference from placebo in LDL-C percent change from baseline was -61.9% (95% CI: -64.3%, -59.4%; p-value: <0.0001). For detailed results see Table 2. At week 12, 82.1% of patients in the Praluent group reached an LDL-C < 1.81 mmol/L compared to 7.2% of patients in the placebo group. Reduction in LDL-C was seen across age, gender, body mass index (BMI), race, and baseline LDL-C levels. Efficacy results were consistent in patients with heFH and non-heFH, patients with mixed dyslipidaemia, and diabetic patients. LDL-C reduction was consistent regardless of concomitantly used statins and doses.

Table 2 - Mean percent change in LDL-C from baseline in LDL-C and other lipids/lipoproteins in placebo-controlled and ezetimibe-controlled studies

Mean Percent Change from Baseline in Placebo-Controlled Studies on Background Statin								
	LONG TERM (N=2310)		FHI and FHII (N=732)		High FH (N=106)		COMBO I (N=311)	
	Placebo	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab
Number of patients	780	1530	244	488	35	71	106	205
Mean Baseline LDL-C in mg/dL (mmol/L)	122.0 (3.16)	122.8 (3.18)	140.9 (3.65)	141.3 (3.66)	201.0 (5.21)	196.3 (5.10)	104.6 (2.71)	100.3 (2.60)
Week 12								
LDL-C (ITT)[a]	1.5	-63.3	5.4	-43.6	-6.6	-46.9	1.1	-46.3
LDL-C (on	1.4	-64.2	5.3	-44.0	-6.6	-46.9	1.7	-47.6

treatment)[b]								
Week 24								
LDL-C (ITT)[a]	0.8	-61.0[c]	7.1	-48.8[d]	-6.6	-45.7[e]	-2.3	-48.2[f]
LDL-C (on treatment)[b]	0.7	-62.8	6.8	-49.3	-6.6	-45.5	-0.8	-50.7
Non-HDL-C	0.7	-51.6	7.4	-42.8	-6.2	-41.9	-1.6	-39.1
Apo B	1.2	-52.8	1.9	-41.7	-8.7	-39.0	-0.9	-36.7
Total-C	-0.3	-37.8	5.5	-31.2	-4.8	-33.2	-2.9	-27.9
Lp(a)	-3.7	-29.3	-8.5	-26.9	-8.7	-23.5	-5.9	-20.5
TG	1.8	-15.6	4.3	-9.8	-1.9	-10.5	-5.4	-6.0
HDL-C	-0.6	4.0	0.2	7.8	3.9	7.5	-3.8	3.5
Apo A-1	1.2	4.0	-0.4	4.2	2.0	5.6	-2.5	3.3

Mean Percent Change from Baseline in Ezetimibe-Controlled Studies				
	On Background Statin		**On Other Lipid Modifying Therapy**	
	COMBO II (N=707)		**ALTERNATIVE (N=248)**	
	Ezetimibe	**Alirocumab**	**Ezetimibe**	**Alirocumab**
Number of patients	240	467	122	126
Mean Baseline LDL-C in mg/dL (mmol/L)	104.5 (2.71)	108.3 (2.81)	194.2 (5.03)	191.1 (5.0)
Week 12				
LDL-C (ITT)[a]	-21.8	-51.2	-15.6	-47.0
LDL-C (on treatment)[b]	-22.7	-52.4	-18.0	-51.2
Week24				
LDL-C (ITT)[a]	-20.7	-50.6[g]	-14.6	-45.0[h]
LDL-C (on treatment)[b]	-21.8	-52.4	-17.1	-52.2
Non-HDL-C	-19.2	-42.1	-14.6	-40.2
Apo B	-18.3	-40.7	-11.2	-36.3
Total-C	-14.6	-29.3	-10.9	-31.8
Lp(a)	-6.1	-27.8	-7.3	-25.9
TG	-12.8	-13.0	-3.6	-9.3
HDL-C	0.5	8.6	6.8	7.7
Apo A-1	-1.3	5.0	2.9	4.8

[a] ITT analysis – intent-to-treat population, includes all lipid data throughout the duration of the study irrespective of adherence to the study treatment

[b] On treatment analysis – analysis restricted to the time period that patients actually received treatment. The % LDL-C reduction at week 24 corresponds to a mean absolute change of:

[c] -74.2 mg/dL (-1.92 mmol/L); [d] -71.1 mg/dL (-1.84 mmol/mL); [e] -90.8 mg/dL (-2.35 mmol/L); [f] -50.3 mg/dL (-1.30 mmol/L); [g] -55.4 mg/dL (1.44 mmol/L); [h] -84.2 mg/dL (-2.18 mmol/L).

INDICATIONS

Praluent is indicated as an adjunct to diet and exercise in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease:

- in combination with a statin, or statin with other lipid-lowering therapies or,
- in combination with other lipid-lowering therapies in patients who are statin-intolerant.

The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined (see CLINICAL TRIALS).

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients

For contraindications related to concomitant statins or other lipid-modifying therapy, please refer to their current respective product information.

PRECAUTIONS

General allergic reactions, including pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in clinical studies (see section ADVERSE EFFECTS). If signs or symptoms of serious allergic reactions occur, treatment with Praluent must be discontinued and appropriate symptomatic treatment initiated.

Immunogenicity

In phase 3 studies, 4.8% of alirocumab-treated patients had a treatment-emergent ADA response as compared to 0.6% in the control group (placebo or ezetimibe). The majority of those patients exhibited transient low-titer ADA responses with no neutralising activity. Compared to patients who were ADA negative, patients with an ADA positive status did not exhibit any difference in

alirocumab exposure, efficacy, or safety, except for a higher rate of injection site reactions. Only 1.2% of patients exhibited neutralising antibodies (NAb), all of them in the alirocumab group. Most of these patients had only one positive neutralising sample. Only 10 patients (0.3%) had two or more NAb positive samples. The data do not suggest a correlation between the presence of NAb and LDL-C lowering efficacy or safety. Immunogenicity data are highly dependent on the sensitivity and specificity of the ADA assay.

LOW LDL-C LEVELS

Although adverse consequences of very low LDL-C were not identified in the clinical trials, the long term effects of very low levels of LDL-C are unknown.

EFFECTS ON FERTILITY

There were no adverse effects of alirocumab on surrogate markers of fertility (e.g. oestrous cycling, testicular volume, ejaculate volume, sperm motility, sperm concentration and total sperm count per ejaculate) in a 26-week toxicity study in sexually-mature monkeys. The highest dose in this study resulted in a serum AUC that was about 100 times that expected in patients at the maximum recommended dose. In addition, there were no alirocumab-related macroscopic or microscopic findings in reproductive organs in any rat or monkey toxicity study.

USE IN PREGNANCY (CATEGORY B1)

There are no data from the use of Praluent in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity.

When pregnant female animals were exposed to alirocumab, measurable alirocumab concentrations in serum were observed in fetal rats (and also infant monkeys), indicating that alirocumab, like other IgG antibodies, crosses the placenta.

There were no effects on fetal growth or development in the rat embryofoetal development study conducted at doses up to 75 mg/kg/dose administered on gestation days 6 and 12. At this dose, serum AUC was about 20 times the AUC expected in patients at the maximum recommended dose.

There was a slight attenuation of secondary anti-KLH IgG antibody response in infant offspring of cynomolgus monkeys dosed with alirocumab during organogenesis to parturition at maternal exposure of 13-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. Alirocumab given at subcutaneous doses of up to 75 mg/kg/week to pregnant monkeys from gestation day 20 until parturition, had no adverse effects on the growth and development of offspring up to 6 months post-birth. At this dose, serum AUC was about 80 fold the AUC expected in patients at the maximum recommended dose.

Animal studies are not always predictive of human response. Therefore, it is not known whether Praluent can cause foetal harm when administered to a pregnant woman and Praluent should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

For use in combination therapy with a statin

Statins are contraindicated in pregnant women. Please refer to the current respective product information.

USE IN LACTATION

It is not known whether alirocumab is excreted in human milk. Because immunoglobulins are excreted in human milk, the use of Praluent is not recommended in breast-feeding women.

For use in combination therapy with a statin

Statins are contraindicated in breast-feeding women. Please refer to the current respective product information.

PAEDIATRIC USE

The safety and efficacy of Praluent in patients below the age of 18 have not been established.

USE IN THE ELDERLY

In controlled studies, 1158 patients (34.7%) treated with Praluent were ≥65 years of age and 241 patients (7.2%) treated with Praluent were ≥75 years of age. There were no significant differences observed in safety and efficacy with increasing age.

HEPATIC IMPAIRMENT

Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Praluent should be used with caution in patients with severe hepatic impairment.

RENAL IMPAIRMENT

In clinical studies, there was limited representation of patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m^2). Praluent should be used with caution in patients with severe renal impairment.

GENOTOXICITY

Genotoxicity studies have not been conducted with alirocumab. As alirocumab is a monoclonal antibody it would not be expected to have genotoxic potential.

CARCINOGENICITY

Carcinogenicity studies have not been conducted with alirocumab.

EFFECT ON LABORATORY TESTS

No interactions with laboratory tests have been identified.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Praluent has no or negligible influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Effects of alirocumab on other medicinal products

Since alirocumab is a biologic, no pharmacokinetic effects of alirocumab on other medicinal products are anticipated. In clinical studies where alirocumab was administered in combination with atorvastatin or rosuvastatin, no relevant changes in statin concentrations were observed in the presence of repeated administration of alirocumab, indicating that cytochrome P450 enzymes (mainly CYP3A4 and CYP2C9) and transporter proteins such as P-gp and OATP were not affected by alirocumab.

Effects of other medicinal products on alirocumab

Statins and other lipid-modifying therapy are known to increase production of PCSK9, the protein targeted by alirocumab. Because a component of the clearance of alirocumab is target-mediated, an elevation in target could lead to lower alirocumab exposure. However, this effect does not impact the duration of efficacy when alirocumab is administered every two weeks.

ADVERSE EFFECTS

The safety data are based on pooled results from nine placebo-controlled studies (four phase 2 and five phase 3 studies, all in patients on background statin), and five ezetimibe-controlled phase 3 studies (with three studies in patients on background statin). This reflects exposure to alirocumab in 3340 patients (3451 patient-years of exposure), the majority with high or very high cardiovascular risk, treated with alirocumab at a dose of 75 or 150 mg, administered subcutaneously once every 2 weeks, for a treatment duration of up to 18 months (including 2408 patients exposed to alirocumab for at least 52 weeks, and 639 patients exposed to alirocumab for at least 76 weeks).

Most common adverse reactions (≥1% of patients treated with Praluent) were local injection site reactions, upper respiratory tract signs and symptoms and pruritus. Most common adverse reactions leading to treatment discontinuation in patients treated with Praluent were local injection site reactions.

No difference in the safety profile was observed between the two doses (75 mg once every 2 weeks and 150 mg once every 2 weeks) used in the phase 3 program.

In controlled studies, 1158 patients (34.7%) treated with Praluent were ≥65 years of age and 241 patients (7.2%) treated with Praluent were ≥75 years of age. There were no significant differences observed in safety and efficacy with increasing age.

Table 3 shows the adverse reactions reported in patients treated with alirocumab in pooled controlled studies.

The frequency categories are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 3 - Adverse reactions reported with Praluent in pooled controlled studies

System Organ Class	Common	Rare
Immune system disorders		hypersensitivity hypersensitivity vasculitis
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract signs and symptoms*	
Skin and subcutaneous tissue disorders	Pruritus	urticaria eczema nummular
General disorders and administration site conditions	Injection site reactions**	

* including mainly oropharyngeal pain, rhinorrhea, sneezing
** including erythema/redness, itching, swelling, pain/tenderness

Table 4 shows the adverse events reported in ≥1% of patients treated with alirocumab and more frequently than with placebo in pooled placebo-controlled studies.

Table 4 - Adverse events occurring in ≥1% of patients treated with alirocumab and more frequently than with placebo in the pool of placebo-controlled trials

Primary System Organ Class Preferred Term n(%)	Placebo (N=1276)	Alirocumab (N=2476)
Infections and infestations		
Nasopharyngitis	11.1%	11.3%
Influenza	4.6%	5.7%
Urinary tract infection	4.6%	4.8%

Primary System Organ Class Preferred Term n(%)	Placebo (N=1276)	Alirocumab (N=2476)
Bronchitis	3.8%	4.3%
Sinusitis	2.7%	3.0%
Gastroenteritis viral	0.7%	1.3%
Pneumonia	1.1%	1.3%
Pharyngitis	0.8%	1.1%
Cellulitis	0.8%	1.0%
Psychiatric disorders		
Insomnia	1.3%	1.4%
Respiratory, thoracic and mediastinal disorders		
Cough	2.3%	2.5%
Oropharyngeal pain	0.5%	1.2%
Metabolism and nutrition disorders		
Diabetes mellitus	1.1%	1.3%
Type 2 diabetes mellitus	0.9%	1.3%
Gout	0.9%	1.1%
Gastrointestinal disorders		
Diarrhoea	4.4%	4.7%
Constipation	1.5%	1.7%
Abdominal pain	1.3%	1.6%
Abdominal pain upper	0.8%	1.1%
Skin and subcutaneous tissue disorders		

Primary System Organ Class Preferred Term n(%)	Placebo (N=1276)	Alirocumab (N=2476)
Pruritus	0.4%	1.1%
Musculoskeletal and connective tissue disorders		
Myalgia	3.4%	4.2%
Muscle spasms	2.4%	3.1%
Musculoskeletal pain	1.6%	2.1%
Cardiac disorders		
Angina unstable	0.9%	1.2%
Vascular disorders		
Hypertension	3.0%	3.1%
General disorders and administration site conditions		
Injection site reaction	5.1%	7.2%
Oedema peripheral	0.9%	1.3%
Investigations		
Alanine aminotransferase increased	0.7%	1.1%
Injury, poisoning and procedural complications		
Contusion	1.3%	2.1%

Local injection site reactions

Local injection site reactions, including erythema/redness, swelling, and pain/tenderness were reported in 6.1% of patients treated with alirocumab versus 4.1% in the control group. Most

injection site reactions were transient and of mild intensity. The discontinuation rate due to local injection site reactions was comparable between the two groups (0.2% in the alirocumab group versus 0.3% in the control group).

General allergic reactions

General allergic reactions were reported more frequently in the alirocumab group than in the control group, mainly due to a difference in the incidence of pruritus. The observed cases of pruritus were typically mild and transient. In addition, rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in controlled clinical studies. (see PRECAUTIONS).

LDL-C values < 0.65 mmol/L

In pooled controlled studies, 796 of 3340 patients (23.8%) treated with Praluent had two consecutive values of LDL-C < 0.65 mmol/L, including 288 patients (8.6%) with two consecutive values < 0.39 mmol/L. These mostly occurred when patients were initiated and maintained on 150 mg once every 2 weeks of Praluent regardless of the baseline LDL-C value or the response to treatment. No adverse reaction was identified related to these LDL-C values. Although adverse consequences of very low LDL-C were not identified in clinical trials, the long term effects of very low levels of LDL-C induced by Praluent are unknown.

Cardiovascular (CV) events

A cardiovascular outcomes trial whose primary endpoint is adjudicated major adverse cardiovascular events (MACE, i.e. CHD death, myocardial infarction, ischemic stroke, and unstable angina requiring hospitalization) is ongoing. The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined (see CLINICAL TRIALS).

In pre-specified analysis of pooled phase 3 studies, treatment-emergent CV events confirmed by adjudication, consisting of coronary heart disease (CHD) death, myocardial infarction, ischemic stroke, unstable angina requiring hospitalization, congestive heart failure hospitalization, and revascularization, were reported in 110 (3.5%) patients in the alirocumab group and 53 (3.0%) patients in the control group (placebo or active control) with HR=1.08 (95% CI, 0.78 to 1.50). MACE confirmed by adjudication were reported in 52 of 3182 (1.6%) patients in the alirocumab

group and 33 of 1792 (1.8%) patients in the control group (placebo or active control); HR=0.81 (95% CI, 0.52 to 1.25).

In pre-specified final analyses of the LONG TERM study, treatment-emergent CV events confirmed by adjudication occurred in 72 of 1550 (4.6%) patients in the alirocumab group and in 40 of 788 (5.1%) patients in the placebo group; MACE confirmed by adjudication were reported in 27 of 1550 (1.7%) patients in the alirocumab group and 26 of 788 (3.3%) patients in the placebo group. Hazard ratios were calculated post-hoc; for all CV events, HR=0.91 (95% CI, 0.62 to 1.34); for MACE, HR=0.52 (95% CI, 0.31 to 0.90).

All-cause mortality

All-cause mortality in phase 3 studies was 0.6% (20 of 3182 patients) in the alirocumab group and 0.9% (17 of 1792 patients) in the control group. The primary cause of death in the majority of these patients was CV events.

Neurocognitive Events

Neurocognitive events were reported in 0.8% of patients treated with alirocumab and 0.7% of patients treated with placebo. Confusion or memory impairment were each reported in 0.2% of patients treated with alirocumab and in <0.1% (for each) in the placebo group patients. The majority of neurocognitive events were non-serious. The causal relationship between these events and alirocumab has not been established.

Post-marketing experience

At this time there is limited post-marketing experience with alirocumab.

DOSAGE AND ADMINISTRATION

The recommended starting dose of Praluent is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage.

If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Lipid levels may be measured from 4 weeks of initiating or titrating Praluent, to assess the response and adjust the dose, if needed.

For mean LDL-C reduction achieved with the 75 mg and 150 mg dose in controlled clinical studies see section CLINICAL TRIALS.

If a dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

No dose adjustments are needed for elderly patients or patients based on weight. No dose adjustments are needed for patients with mild or moderate renal or hepatic impairment (see PHARMACOKINETICS)

Method of Administration

Praluent is injected as a single subcutaneous injection into the thigh, abdomen or upper arm. It is recommended to rotate the injection site with each injection. Praluent should not be injected into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

The patient may either self-inject Praluent or a caregiver may administer Praluent, after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

Praluent must not be co-administered with other injectable medicinal products at the same injection site.

Praluent is a sterile product and contains no antimicrobial preservatives. Product is for single use in one patient only.

Before administration, Praluent should be inspected visually for particulate matter and discolouration. If the solution is discoloured or contains particulate matter, the solution should not be used.

To avoid discomfort, Praluent should be allowed to warm to room temperature (up to 25°C) for 30 to 40 minutes prior to use. Do not heat, let it warm up on its own. Praluent should be used as soon as possible after it has warmed up. Time out of refrigeration should not exceed 24 hours at 25°C.

After use, place the Praluent pre-filled pen or pre-filled syringe into a puncture resistant container and discard in accordance with local requirements.

OVERDOSAGE

In controlled clinical studies, no safety issues were identified with more frequent dosing than the recommended once every 2 weeks dosing schedule.

Contact the Australian Poisons Information Centre (telephone 13 11 26), or the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Praluent is supplied as a sterile, clear, colourless to pale yellow solution for injection, in a single use pre-filled pen or single-use pre-filled syringe, containing no antimicrobial preservatives.

Praluent 75 mg/mL and 150 mg/mL solution for injection is supplied in a siliconised 1 ml Type 1 clear glass syringe, equipped with a stainless steel needle, a styrene-butadiene rubber soft needle shield (does not contain natural latex), and a coated bromobutyl rubber plunger stopper.

Pre-filled pen

75 mg/mL pre-filled syringe components are assembled into a pen with a blue cap and a light green activation button. Available in pack sizes of 1, 2 or 6 per carton.

150 mg/mL pre-filled syringe components are assembled into a pen with a blue cap and a dark grey activation button. Available in pack sizes of 1, 2 or 6 per carton.

Pre-filled syringe

75 mg/mL pre-filled syringe is equipped with a light green polypropylene plunger rod. Available in pack sizes of 1, 2 or 6 per carton.

150 mg/mL pre-filled syringe is equipped with a dark grey polypropylene plunger rod. Available in pack sizes of 1, 2 or 6 per carton.

Store at 2°C to 8°C (Refrigerate. Do not freeze). Do not expose to extreme heat. Keep in the outer carton in order to protect from light.

* Presentations currently not marketed

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

17 May 2016

DATE OF MOST RECENT AMENDMENT

Praluent® is a registered trademark of Sanofi.